22.

No 2

CHEMICAL CONSTITUTION AND HYPNOTIC ACTION. ACID AMIDES AND PRODUCTS OF THE CONDENSATION OF MALONAMIDES AND MALONIC ESTERS.

BY

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LXIX.—*Chemical Constitution and Hypnotic Action. Acid Amides and Products of the Condensation of Malonamides and Malonic Esters.*

ROYAL COLLEGE OF SURGEONS OF ENGLAND

By Frederic George Percy Remfry.

The original idea of the work described in this paper was to study the changes in hypnotic effect produced by substituting the hydrogen of the amido-group in acid amides by various radicles. The physiological testing of the compounds was carried out by Dr. H. H. Dale at the Wellcome Physiological Research Laboratories, to whom the author desires to express his thanks. It may be at once mentioned that not one of these substances possessed any hypnotic properties whatever, and consequently the object of the investigation was not attained. The inactivity of these compounds is, at first sight, surprising, in view of the number of alkyl groups contained in some of them, and it is therefore probable that they are insoluble in lipoid substances, and that this —in the sense of the Overton-Meyer hypothesis—is responsible for their inactivity.

Many acid amides have already been tested physiologically (Nebenthau, *Arch. exp. Path. Pharm.*, 1895, **36**, 451), and have been found to be, in general, of weak hypnotic power, at the same time producing cramps similar to those induced by ammonia. The latter effect is found to be increased by substituting the hydrogen of the amido-group by alkyl radicles, but the narcotic power of the drug is thereby lessened. Consequently, in the present work only such substances, as a rule, were used for substituents as are already known to possess hypnotic properties of their own in some degree.

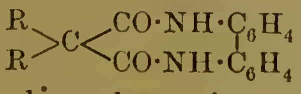
The four substances, *dicinnamoylcarbamide*,

$$(C_6H_5\cdot CH{:}CH\cdot CO\cdot NH)_2CO,$$

ethyl cinnamoylcarbamate, $C_6H_5\cdot CH{:}CH\cdot CO\cdot NH\cdot CO_2Et$, *cinnamoyl*-p-*aminoacetophenone*, $C_6H_5\cdot CH{:}CH\cdot CO\cdot NH\cdot C_6H_4\cdot CO\cdot CH_3$, and α-*bromo*iso*valeryl*-p-*aminoacetophenone*,

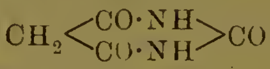
$$CHMe_2\cdot CHBr\cdot CO\cdot NH\cdot C_6H_4\cdot CO\cdot CH_3,$$

can be regarded as acid amides in which one hydrogen of the amido-group has been displaced by a radicle which (except in the first instance) is known to have hypnotic properties, and yet the resulting products were absolutely inactive.

Several substances of the type  $\begin{matrix}R\\R\end{matrix}\!>\!C\!<\!\begin{matrix}CO\cdot NH\cdot C_6H_4\\CO\cdot NH\cdot C_6H_4\end{matrix}$ (R = alkyl) were prepared, but were found to be useless owing to their almost complete insolubility in all solvents.

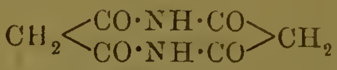
The next step led to some interesting results on the effect produced on the general properties of ethyl malonate and malonamide by the introduction of various alkyl radicles, as will be explained later.

It is well known that it is necessary to introduce two ethyl groups into the molecule of barbituric acid (I) in order to impart to it its narcotic power, a methylethyl or ethyl group, or two methyl groups being insufficient. From this it was thought probable that the introduction of more than two ethyl groups into a somewhat similarly constituted molecule would still further increase the hypnotic effect. With this in view, condensation between malonamide and ethyl malonate was brought about by means of sodium ethoxide, a cyclic compound, *malonylmalonamide* (II), being formed:



$\mathrm{CH_2}{<}\begin{matrix}\mathrm{CO\cdot NH}\\ \mathrm{CO\cdot NH}\end{matrix}{>}\mathrm{CO}$

(I.)

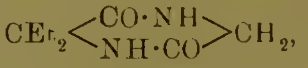
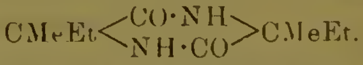


$\mathrm{CH_2}{<}\begin{matrix}\mathrm{CO\cdot NH\cdot CO}\\ \mathrm{CO\cdot NH\cdot CO}\end{matrix}{>}\mathrm{CH_2}$

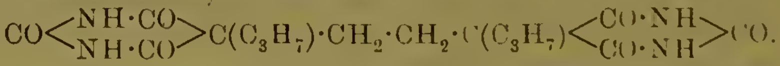
(II.)

The formation of this compound is similar to that of the dialkylbarbituric acids from carbamide and ethyl alkylmalonates (Fischer and Dilthey, *Annalen*, 1904, **335**, 334), and from dialkylmalonamides and ethyl carbonate (D.R.-P. 163136). The general properties of this compound are also in agreement with those that would be expected of a substance having such a formula.

A number of alkyl derivatives of this substance have been prepared by direct alkylation; none of them, however, possessed any hypnotic properties, although resembling diethylbarbituric acid (veronal) structurally to some extent.

An analogous case to this is to be found in a recent paper by Rosenmund (*Ber.*, 1909, **42**, 4470), where the preparation of diketodiethylpiperazine,  $\mathrm{CEt_2}{<}\begin{matrix}\mathrm{CO\cdot NH}\\ \mathrm{NH\cdot CO}\end{matrix}{>}\mathrm{CH_2}$, is described. This substance closely resembles diethylbarbituric acid, but possesses no hypnotic properties whatever; neither were any observed when four alkyl radicles were introduced, as in 3:6-diketo-2:5-dimethyl-2:5-diethylpiperazine,  $\mathrm{CMeEt}{<}\begin{matrix}\mathrm{CO\cdot NH}\\ \mathrm{NH\cdot CO}\end{matrix}{>}\mathrm{CMeEt}$.

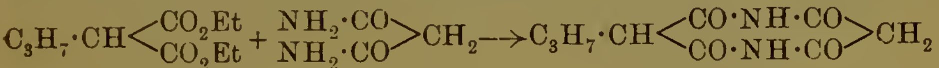
It has now been found that *ethylenebis-5-propylbarbituric acid*,



$\mathrm{CO}{<}\begin{matrix}\mathrm{NH\cdot CO}\\ \mathrm{NH\cdot CO}\end{matrix}{>}\mathrm{C(C_3H_7)\cdot CH_2\cdot CH_2\cdot C(C_3H_7)}{<}\begin{matrix}\mathrm{CO\cdot NH}\\ \mathrm{CO\cdot NH}\end{matrix}{>}\mathrm{CO}$,

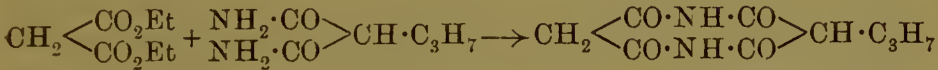
which may be regarded as two molecules of monopropylbarbituric acid joined together by an ethylene linking, was also quite inactive.

With the idea of proving the constitution of the different compounds obtained by alkylating malonylmalonamide, it was first ascertained, by heating with hydriodic acid to 300° according to the Herzig-Meyer method, that all the alkyl groups were directly attached to carbon. Various condensations between alkyl substituted malonic esters and amides were then carried out, and it was expected that both the condensation products of, for example, (III), ethyl propylmalonate and malonamide, and (IV), ethyl malonate and propylmalonamide, would give one and the same product as (V), namely, that obtained by the introduction of one propyl radicle into malonylmalonamide, thus:



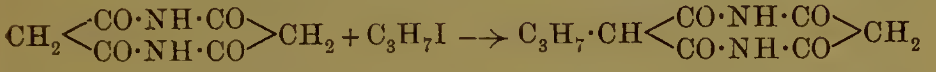
$$C_3H_7\cdot CH<\begin{matrix}CO_2Et\\CO_2Et\end{matrix}+\begin{matrix}NH_2\cdot CO\\NH_2\cdot CO\end{matrix}>CH_2\longrightarrow C_3H_7\cdot CH<\begin{matrix}CO\cdot NH\cdot CO\\CO\cdot NH\cdot CO\end{matrix}>CH_2$$

(III.)



$$CH_2<\begin{matrix}CO_2Et\\CO_2Et\end{matrix}+\begin{matrix}NH_2\cdot CO\\NH_2\cdot CO\end{matrix}>CH\cdot C_3H_7\longrightarrow CH_2<\begin{matrix}CO\cdot NH\cdot CO\\CO\cdot NH\cdot CO\end{matrix}>CH\cdot C_3H_7$$

(IV.)

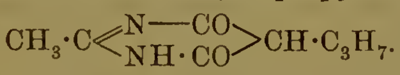


$$CH_2<\begin{matrix}CO\cdot NH\cdot CO\\CO\cdot NH\cdot CO\end{matrix}>CH_2+C_3H_7I\longrightarrow C_3H_7\cdot CH<\begin{matrix}CO\cdot NH\cdot CO\\CO\cdot NH\cdot CO\end{matrix}>CH_2$$

(V.)

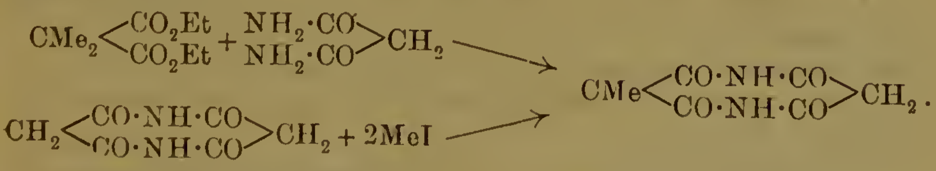
The product, *propylmalonylmalonamide*, obtained by propylating malonylmalonamide according to reaction (V), proved to be identical with the condensation product of ethyl propylmalonate and malonamide, as shown by reaction (III), and it is therefore clear that the alkyl radicle in the former reaction attaches itself to one of the methylene groups.

The condensation, however, of ethyl malonate and propylmalonamide did not proceed as depicted above in reaction (IV), but resulted in the production of a compound which proved, on analysis, to contain one molecule of carbon dioxide less than propylmalonylmalonamide, and which, from considerations to be given later, was considered to be 4:6-*diketo*-2-*methyl*-5-*propyltetrahydropyrimidine*,



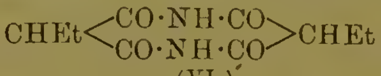
$$CH_3\cdot C\begin{matrix}\nearrow N - CO\\ \searrow NH\cdot CO\end{matrix}>CH\cdot C_3H_7.$$

It now remained to ascertain the position of the two other alkyl groups which it was found possible to introduce into the molecule of malonylmalonamide. That of the second was proved in the following way. Ethyl dimethylmalonate and malonamide, when condensed together, were found to give a compound identical with that obtained when two methyl groups are introduced into malonylmalonamide, thus:



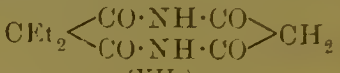
$$\left.\begin{matrix}CMe_2<\begin{matrix}CO_2Et\\CO_2Et\end{matrix}+\begin{matrix}NH_2\cdot CO\\NH_2\cdot CO\end{matrix}>CH_2\longrightarrow\\[1em] CH_2<\begin{matrix}CO\cdot NH\cdot CO\\CO\cdot NH\cdot CO\end{matrix}>CH_2+2MeI\longrightarrow\end{matrix}\right. CMe<\begin{matrix}CO\cdot NH\cdot CO\\CO\cdot NH\cdot CO\end{matrix}>CH_2.$$

It could not be proved by a similar experiment that two ethyl or propyl groups enter the malonylmalonamide molecule in the same way as the two methyl groups, owing to the condensation between ethyl diethyl- (or dipropyl-) malonate and malonamide proceeding in a different manner from that occurring in the case of ethyl dimethylmalonate. Proof, however, that the higher alkyl groups attach themselves in a similar manner to the methyl groups was obtained was follows. There are two possible formulæ for the *diethylmalonylmalonamide* obtained by ethylation, namely, the symmetrical (VI) and the unsymmetrical (VII):



$$\mathrm{CHEt}<\begin{matrix}\mathrm{CO\cdot NH\cdot CO}\\ \mathrm{CO\cdot NH\cdot CO}\end{matrix}>\mathrm{CHEt}$$

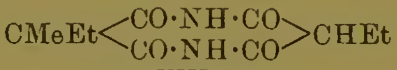
(VI.)



$$\mathrm{CEt_2}<\begin{matrix}\mathrm{CO\cdot NH\cdot CO}\\ \mathrm{CO\cdot NH\cdot CO}\end{matrix}>\mathrm{CH_2}$$

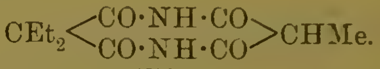
(VII.)

These, on methylation, will yield respectively *methylethylmalonylethylmalonamide* (VIII) and *diethylmalonylmethylmalonamide* (IX):



$$\mathrm{CMeEt}<\begin{matrix}\mathrm{CO\cdot NH\cdot CO}\\ \mathrm{CO\cdot NH\cdot CO}\end{matrix}>\mathrm{CHEt}$$

(VIII.)

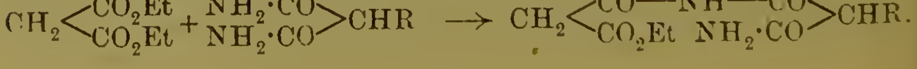


$$\mathrm{CEt_2}<\begin{matrix}\mathrm{CO\cdot NH\cdot CO}\\ \mathrm{CO\cdot NH\cdot CO}\end{matrix}>\mathrm{CHMe.}$$

(IX.)

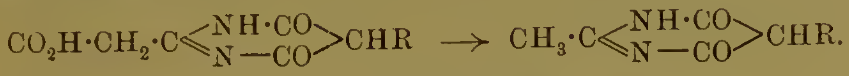
Now the product of condensation of ethyl methylethylmalonate and malonamide is *methylethylmalonylmalonamide*, and yields, on ethylation, *methylethylmalonylethylmalonamide*. This is not identical with the substance obtained by methylation of diethylmalonylmalonamide, which must, therefore, have a formula represented by (VII), and is diethylmalonylmalonamide. It has already been mentioned that when ethyl malonate was condensed with propylmalonamide, the reaction did not proceed as when using malonamide itself, but resulted in the formation of a pyrimidine derivative. Further experiments showed that in every case where an alkyl substituted malonamide of the type $\mathrm{NH_2\cdot CO\cdot CHR\cdot CO\cdot NH_2}$ was condensed with ethyl malonate or ethyl monoalkylmalonate, a similar pyrimidine ring was formed, an increase in size of the substituting group from methyl to propyl having apparently no further influence on the course of the reaction. Now Fischer and Dilthey (*Ber.*, 1902, **35**, 844) have shown that the formation of malonamides increases in difficulty progressively with the size and number of alkyl groups introduced into the molecule of ethyl malonate. This clearly shows that the character of malonamide must be greatly changed by the entrance of alkyl groups, and accounts for the variation in the course of the reaction when condensing ethyl malonate with alkylmalonamides in place of malonamide itself.

The course of the condensation in the formation of pyrimidines is probably as follows. Condensation first takes place between one ester and amido-group:



$$\mathrm{CH_2}<\begin{matrix}\mathrm{CO_2Et}\\ \mathrm{CO_2Et}\end{matrix}+\begin{matrix}\mathrm{NH_2\cdot CO}\\ \mathrm{NH_2\cdot CO}\end{matrix}>\mathrm{CHR}\longrightarrow\mathrm{CH_2}<\begin{matrix}\mathrm{CO{-}\!\!-NH{-}\!\!-CO}\\ \mathrm{CO_2Et\quad NH_2\cdot CO}\end{matrix}>\mathrm{CHR.}$$

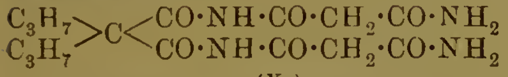
Water is then split off with closing of the ring, and hydrolysis of the remaining ester, and subsequent elimination of carbon dioxide, next occurs:



$$\mathrm{CO_2H\cdot CH_2\cdot C}\left<\begin{matrix}\mathrm{NH\cdot CO}\\ \mathrm{N - CO}\end{matrix}\right>\mathrm{CHR} \longrightarrow \mathrm{CH_3\cdot C}\left<\begin{matrix}\mathrm{NH\cdot CO}\\ \mathrm{N - CO}\end{matrix}\right>\mathrm{CHR}.$$

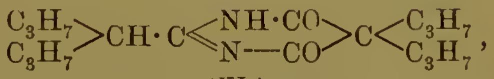
A similar loss of carbon dioxide, due to the action of sodium ethoxide, was observed by Einhorn (*Annalen*, 1908, **359**, 145), who found that the anhydride of diethylmalonic acid, when thus treated, gave ethyl diethylmalonate, ethyl hydrogen diethylmalonate, and ethyl diethylacetate.

The condensation of malonamides with malonyl chlorides leads to results similar to those obtained with the esters. In the case of the unsubstituted malonamide, a normal condensation product is obtained, but dialkylmalonamides again yield condensation products, from which carbon dioxide has been eliminated. Thus dipropylmalonyl chloride and malonamide (2 mols.) give *dipropylmalonyldimalonamide* (X), whilst the same acid chloride and dipropylmalonamide give 4:6-*diketo*-5:5-*dipropyl*-2-α-*propylbutyltetrahydropyrimidine* (XI):



$$\begin{matrix}\mathrm{C_3H_7}\\ \mathrm{C_3H_7}\end{matrix}\!>\mathrm{C}<\!\begin{matrix}\mathrm{CO\cdot NH\cdot CO\cdot CH_2\cdot CO\cdot NH_2}\\ \mathrm{CO\cdot NH\cdot CO\cdot CH_2\cdot CO\cdot NH_2}\end{matrix}$$

(X.)



$$\begin{matrix}\mathrm{C_3H_7}\\ \mathrm{C_3H_7}\end{matrix}\!>\mathrm{CH\cdot C}\left<\begin{matrix}\mathrm{NH\cdot CO}\\ \mathrm{N - CO}\end{matrix}\right>\mathrm{C}<\!\begin{matrix}\mathrm{C_3H_7}\\ \mathrm{C_3H_7}\end{matrix},$$

(XI.)

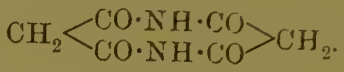
the formation of the latter being analogous to that of the pyrimidine depicted in the last equation.

It has now been shown that an eight-membered ring is not formed when malonic ester or a substituted malonic ester is condensed with a substituted malonamide, but only when it is condensed with malonamide itself. Even the latter reaction, however, has its limits, malonamide condensing readily only with monoalkyl- and dimethyl-malonic esters. With methylethylmalonic esters it condenses to the eight-membered ring only with difficulty, and with diethyl- and higher dialkyl-malonic esters condensation takes place with the formation of substances which have entirely different properties from either the malonylmalonamide or pyrimidine compounds.

In this connexion the results of Meyer (*Ber.*, 1906, **39**, 198) on the influence of the size of alkyl groups on the formation of amides from malonic esters are of interest. He shows that in a disubstituted malonic ester at least two ethyl groups, either in the esters or attached to the quaternary carbon atom, are necessary to prevent reaction between the ester and aqueous ammonia. In the present case, at least two ethyl groups, attached to the quaternary carbon atom only, are necessary to prevent a normal condensation with malonamide, the alkyl groups forming the esters apparently having no influence on the course of the reaction.

EXPERIMENTAL.

Malonylmalonamide,



$CH_2 <\begin{matrix} CO \cdot NH \cdot CO \\ CO \cdot NH \cdot CO \end{matrix}> CH_2$.

Ethyl malonate (1 mol.) and malonamide (1¼ mols.), together with sodium (4 atoms) dissolved in twenty times its weight of absolute alcohol, were heated under pressure in a soda-water bottle for five hours in a brine-bath at 105—107°. When cold, the contents of the bottle were poured on a filter, and the colourless residue, after being washed with absolute alcohol, was dissolved in as little water as possible, and the solution just acidified by careful addition of concentrated hydrochloric acid. A colourless solid at once began to separate, and precipitation was complete in the course of a few hours. The solid was collected, washed with water, and crystallised from hot water. Colourless, crystalline, nodular masses were obtained, which melted and decomposed at 252—253°, after drying at 110°.

The alcoholic filtrate from the reaction mass was evaporated to dryness on the water-bath, the residue dissolved in a little water, and, on acidifying, a certain amount of colourless solid was precipitated. The yield in this case amounted to about 30 per cent. of the theoretical after crystallisation. When, however, substituted malonic esters or malonamides were employed, the yield decreased rapidly, and in many cases was very poor indeed.

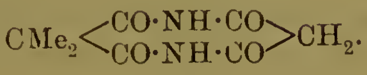
In all condensations of this type, which are described later, the method employed was identical with this one. No details will, therefore, be necessary in future cases:

0·1106 gave 0·1720 CO_2 and 0·0366 H_2O. C=42·4; H=3·7.
0·1200 ,, 16·2 c.c. N_2 at 19° and 784 mm. N=16·4.
1·1707 (air-dried) lost 0·2018 at 110°. H_2O=20·8.
$C_6H_6O_4N_2$ requires C=42·36; H=3·53; N=16·5 per cent.
$C_6H_6O_4N_2,2H_2O$ requires H_2O=18·8 per cent.

This substance is readily soluble in alcohol or acetone, moderately so in hot, but practically insoluble in cold, water. Dilute alkali hydroxides immediately dissolve it, the compound being reprecipitated unchanged by the addition of acids.

The *sodium* salt is a pink, crystalline substance, and is obtained on mixing alcoholic solutions of malonylmalonamide and sodium hydroxide:

0·1957 gave 0·1240 Na_2SO_4. Na = 20·93.
$C_6H_4O_4N_2Na_2$ requires Na = 21·5 per cent.



Dimethylmalonylmalonamide, $CMe_2<\substack{CO\cdot NH\cdot CO\\ CO\cdot NH\cdot CO}>CH_2$.

Ethyl dimethylmalonate (1 mol.), malonamide (1 mol.), and sodium (2 atoms), in absolute alcohol, were condensed as usual. From both the solid and the filtrate from the reaction mixture, a similar compound was obtained, which, after crystallisation from hot water, gave fine, colourless, needle-shaped crystals, melting at 206—207°:

0·1066 gave 0·1890 CO_2 and 0·0482 H_2O. C = 48·36; H = 5·06.
0·1458 „ 18 c.c. N_2 at 21° and 746 mm. N = 14·1.
$C_8H_{10}O_4N_2$ requires C = 48·5; H = 5·05; N = 14·1 per cent.

Dimethylmalonylmalonamide can also be prepared by acting on a dilute alcoholic solution of the sodium salt of malonylmalonamide with excess of methyl iodide exactly as described later in the formation of diethylmalonylmalonamide.

Methylethylmalonylmalonamide.

The quantities employed and the method of condensation were the same as in the last case, but the results were rather different. The alcoholic filtrate from the reaction mass, on treatment as usual, gave an oil, which slowly became crystalline, and, after recrystallisation from alcohol, was obtained in colourless needles, melting at 169—170°:

0·1194 gave 0·2242 CO_2 and 0·0604 H_2O. C = 51·2; H = 5·66.
0·1354 „ 16 c.c. N_2 at 17° and 750 mm. N = 13·8.
$C_9H_{12}O_4N_2$ requires C = 50·9; H = 5·7; N = 13·2 per cent.

The solid substance collected from the reaction mixture under the usual treatment gave a light yellow solid, which crystallised in colourless, nodular masses from a large volume of hot water. This compound does not melt, but burns completely when heated on platinum foil:

0·1098 gave 0·1850 CO_2 and 0·0412 H_2O. C = 45·9; H = 4·2.
0·1198 „ 19·2 c.c. N_2 at 18° and 770 mm. N = 19·2.
$C_{14}H_{15}O_7N_5$ requires C = 46·0; H = 4·1; N = 19·2 per cent.

It has quite different properties from those of methylethylmalonylmalonamide, and evidently does not contain the malonylmalonamide ring.

Diethylmalonylmalonamide.

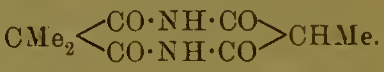
Sodium (2 atoms) was dissolved in thirty times its weight of alcohol, finely powdered malonylmalonamide (1 mol.) added, and the solution heated on the water-bath. The sodium compound which was formed, being insoluble in alcohol, was brought into solution by the cautious addition of water. Ethyl iodide (3 mols.) was then added slowly, and boiling was continued for three hours. Excess of alcohol was removed, and, on cooling, a colourless solid separated; this was collected, dissolved in hot water, and precipitated by the addition of dilute hydrochloric acid. The precipitate was washed with water, and crystallised from dilute alcohol, when colourless prisms, melting at 175—176°, were obtained. On acidifying the original mother liquors with hydrochloric acid, a gelatinous mass was precipitated, which slowly became crystalline. On recrystallisation from dilute alcohol, colourless prisms, melting at 175—176°, identical with the above, were obtained. The total yield was about equal to the weight of malonylmalonamide taken, by far the larger portion being furnished by the acidified mother liquors. This substance is readily soluble in alcohol, acetone, or ether, moderately so in hot, and insoluble in cold, water. It is dissolved by alkali hydroxides, and is reprecipitated by acids unchanged:

0·1287 gave 0·2516 CO_2 and 0·0743 H_2O. C = 53·3; H = 6·4.
0·1778 „ 19·0 c.c. N_2 at 14° and 744 mm. N = 12·5.
$C_{10}H_{14}O_4N_2$ requires C = 53·1; H = 6·2; N = 12·4 per cent.

The *sodium* salt crystallises from alcohol in colourless needles:

0·2022 (air-dried) gave 0·0556 Na_2SO_4. Na = 8·9.
0·2390 „ lost 0·0074 at 120°. H_2O = 3·1.
$C_{10}H_{13}O_4N_2Na,\frac{1}{2}H_2O$ requires Na = 8·9; H_2O = 3·5 per cent.

Dimethylmalonylmethylmalonamide,


$CMe_2{<}\begin{matrix}CO\cdot NH\cdot CO\\ CO\cdot NH\cdot CO\end{matrix}{>}CHMe.$

This was obtained by acting on a solution of dimethylmalonylmalonamide in dilute sodium hydroxide with methyl sulphate in the cold in the usual manner. The solid which separated out was collected, washed with water, and crystallised from benzene. It forms colourless needles, melting at 133°:

0·1140 gave 0·2146 CO_2 and 0·0584 H_2O. C = 51·3; H = 5·74.
0·1464 „ 16 c.c. N_2 at 17° and 772 mm. N = 13·2.
$C_9H_{12}O_4N_2$ requires C = 50·9; H = 5·7; N = 13·2 per cent.

Diethylmalonylmethylmalonamide.

This was prepared from diethylmalonylmalonamide in the same manner as the last substance. The resulting crystalline precipitate was washed with water and crystallised from dilute acetic acid, when long, colourless prisms, melting at 118—119°, were obtained:

0·1074 gave 0·2156 CO_2 and 0·0639 H_2O. C = 54·6; H = 6·6.
0·1158 „ 12·3 c.c. N_2 at 20° and 750 mm. N = 12·3.
$C_{11}H_{16}O_4N_2$ requires C = 55·0; H = 6·7; N = 11·6 per cent.

Methylethylmalonylethylmalonamide.

The interaction of ethyl sulphate and methylethylmalonylmalonamide proceeded very slowly, and nothing separated out. The solution was acidified and extracted with ether, and a colourless oil was obtained, which slowly crystallised, and, after recrystallisation from xylene, gave colourless, prismatic needles, melting at 148—149°:

0·1029 gave 0·2078 CO_2 and 0·0598 H_2O. C = 55·0; H = 6·45.
$C_{11}H_{16}O_4N_2$ requires C = 55·0; H = 6·7 per cent.

All these three last-mentioned substances are soluble in alkali hydroxides, but efforts at further methylation were attended with no success.

Diethylmalonylethylmalonamide.

A warm solution of diethylmalonylmalonamide in sodium hydroxide was treated with ethyl sulphate in the usual way. The solid obtained on acidifying proved to be mostly unchanged diethylmalonylmalonamide, with very little of the ethylated product. This was obtained, after several crystallisations from dilute acetic acid, in straw-coloured plates, melting at 88—89°.

Boiling an alcoholic suspension of the sodium salt of diethylmalonylmalonamide with sodium ethyl sulphate gave no better yield, and all attempts to obtain a tetraethyl compound were unsuccessful:

0·1196 gave 0·2484 CO_2 and 0·0771 H_2O. C = 56·64; H = 7·2.
$C_{12}H_{18}O_4N_2$ requires C = 56·7; H = 7·1 per cent.

Dipropylmalonylmalonamide.

The reaction was carried out exactly as in the case of the diethyl compound. The compound crystallises from dilute acetic acid in colourless needles, melting at 209—210°:

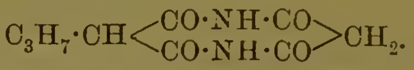
0·1182 gave 0·2448 CO_2 and 0·0778 H_2O. C = 56·4; H = 7·37.
0·1335 „ 13·4 c.c. N_2 at 23° and 762 mm. N = 11·7.
$C_{12}H_{18}O_4N_2$ requires C = 56·7; H = 7·1; N = 11·0 per cent.

Propylmalonylmalonamide.

The original mother liquors from the last-mentioned substance were acidified, the resulting precipitate collected, washed with water, and crystallised from acetic acid, when colourless prisms, melting at 188—189°, were obtained:

0·1107 gave 0·2057 CO_2 and 0·0582 H_2O. C = 50·7; H = 5·9.
0·1254 ,, 14 c.c. N_2 at 17° and 745 mm. N = 13·0.
$C_9H_{12}O_4N_2$ requires C = 50·9; H = 5·7; N = 13·2 per cent.

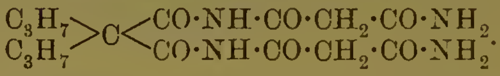
The empirical formula corresponds with the introduction of only one propyl radicle into the molecule of malonylmalonamide, and is thus represented by the formula:



$$C_3H_7\cdot CH\left<\begin{matrix}CO\cdot NH\cdot CO\\ CO\cdot NH\cdot CO\end{matrix}\right>CH_2.$$

Proof of the correctness of this is afforded by the fact that when ethyl propylmalonate is condensed in the usual way with malonamide, a substance is obtained which is identical in all respects with the above compound.

Dipropylmalonyldimalonamide,



$$\left.\begin{matrix}C_3H_7\\ C_3H_7\end{matrix}\right>C\left<\begin{matrix}CO\cdot NH\cdot CO\cdot CH_2\cdot CO\cdot NH_2\\ CO\cdot NH\cdot CO\cdot CH_2\cdot CO\cdot NH_2\end{matrix}\right..$$

Dipropylmalonyl chloride (1 mol.) and malonamide (2 mols.) were well mixed in a flask furnished with an air condenser, and heated in an oil-bath at 110—120° for seven hours. Three times the volume of benzene was then added, and boiling continued for an hour, after which the hot benzene was decanted, and the residue dried under diminished pressure at 100°. It was then extracted several times with hot water. This substance, being insoluble in all the usual organic solvents and water, could not be obtained in a crystalline form, but only as a colourless powder:

0·1013 gave 0·1870 CO_2 and 0·0560 H_2O. C = 50·35; H = 6·2.
0·1330 ,, 18·2 c.c. N_2 at 17° and 748 mm. N = 15·9.
$C_{15}H_{24}O_6N_4$ requires C = 50·57; H = 6·7; N = 15·7 per cent.

Condensation of Ethyl Diethylmalonate and Malonamide.

The ester (1 mol.), the amide (1 mol.), and sodium (3 atoms) were condensed in the usual way. On acidifying the aqueous solution of the solid part of the reaction mixture, a pale yellow, amorphous solid was precipitated. All attempts at obtaining this substance in a crystalline form were fruitless, it being extremely insoluble in organic solvents and water. The mother liquors from the above compound slowly deposited colourless. prismatic crystals, which were recrystallised from hot water. This substance has no melting point, but burns completely when heated on platinum foil:

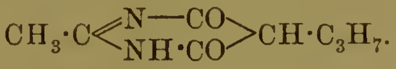
0·1000 gave 0·1598 CO_2 and 0·0388 H_2O. C=43·58; H=4·33.
0·0954 „ 19·5 c.c. N_2 at 21° and 760 mm. N=23·9.
$C_{17}H_{20}O_8N_8$ requires C=43·9; H=4·3; N=24·1 per cent.

Condensation of Methyl Diethylmalonate and Malonamide.

The methyl ester was here substituted for the ethyl ester. This, however, had no effect on the course of the reaction, and the crystalline product was identical with that obtained in the last case:

0·1128 gave 0·1792 CO_2 and 0·0406 H_2O. C=43·34; H=4·03.
0·1051 „ 0·1658 CO_2 „ 0·0394 H_2O. C=43·02; H=4·2.
0·1270 „ 25·9 c.c. N_2 at 17° and 768 mm. N=24·4.
$C_{17}H_{20}O_8N_8$ requires C=43·9; H=4·3; N=24·1 per cent.

4 : 6-*Diketo-2-methyl-5-propyltetrahydropyrimidine*,



$$CH_3\cdot C{<}\begin{array}{l}N{-\!-}CO\\ NH\cdot CO\end{array}{>}CH\cdot C_3H_7.$$

Propylmalonamide (1 mol.), ethyl malonate (1 mol.), and sodium (3 atoms) were condensed and worked up as usual. The product crystallised from acetic acid in colourless needles, which did not melt at 300°. They are insoluble in dilute hydrochloric acid, hot or cold, but readily soluble in cold dilute sodium hydroxide:

0·1183 gave 0·2482 CO_2 and 0·0802 H_2O. C=57·2; H=7·5.
$C_8H_{12}O_2N_2$ requires C=57·1; H=7·1 per cent.

4 : 6-*Diketo-5-methyl-2-ethyltetrahydropyrimidine.*

Prepared from methylmalonamide and ethyl methylmalonate in the same manner as the last substance. The compound crystallises from acetic acid in clusters of colourless, prismatic needles, which do not melt at 300°:

0·1145 gave 0·2265 CO_2 and 0·0694 H_2O. C=53·9; H=6·7.
0·1002 „ 15·4 c.c. N_2 at 15° and 748 mm. N=18·1.
$C_7H_{10}O_2N_2$ requires C=54·4; H=6·5; N=18·2 per cent.

4 : 6-*Diketo-5-ethyl-2-propyltetrahydropyrimidine.*

Prepared from ethylmalonamide and ethyl ethylmalonate. The compound crystallises from dilute acetic acid in colourless, needle-shaped prisms, which do not melt at 300°:

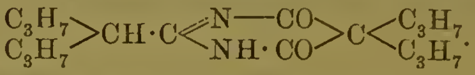
0·1311 gave 0·2860 CO_2 and 0·0904 H_2O. C=59·5; H=7·6.
0·1160 „ 15 c.c. N_2 at 22° and 770 mm. N=15·3.
$C_9H_{14}O_2N_2$ requires C=59·3; H=7·7; N=15·4 per cent.

4 : 6-*Diketo*-5-*propyl*-2-*butyltetrahydropyrimidine.*

Prepared from propylmalonamide and ethyl propylmalonate. It crystallises from dilute acetic acid in small, colourless prisms, not melting at 300°:

0·1352 gave 0·3082 CO_2 and 0·1032 H_2O. C = 62·1; H = 8·5.
0·1314 ,, 15 c.c. N_2 at 25° and 770 mm. N = 13·3.
$C_{11}H_{18}O_2N_2$ requires C = 62·9; H = 8·6; N = 13·3 per cent.

4 : 6-*Diketo*-5 : 5-*dipropyl*-2-α-*propylbutyltetrahydropyrimidine*,



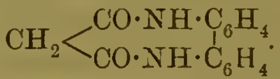
$$\begin{matrix}C_3H_7\\C_3H_7\end{matrix}\!>CH\cdot C\!\begin{matrix}\nearrow N—CO\searrow\\ \searrow NH\cdot CO\nearrow\end{matrix}\!C\!<\!\begin{matrix}C_3H_7\\C_3H_7\end{matrix}.$$

This substance was prepared in a different way from the foregoing pyrimidine derivatives. Equimolecular quantities of dipropylmalonamide and dipropylmalonyl chloride were heated together on the water-bath for sixteen hours, care being taken to exclude moisture. The resulting yellow, jelly-like substance was washed with water and pressed on porous plate. When dry, it was dissolved in cold benzene, in which it is readily soluble, filtered from some insoluble matter, the benzene removed by evaporation, and the residue crystallised from acetic acid. Fine, long, colourless needles were obtained, which melt at 130—131°.

This compound is insoluble in both sodium hydroxide and hydrochloric acid, whether dilute, strong, cold or hot:

0·1096 gave 0·2778 CO_2 and 0·1024 H_2O. C = 69·1; H = 10·3.
0·1212 ,, 9·7 c.c. N_2 at 20° and 763 mm. N = 9·43.
$C_{17}H_{30}O_2N_2$ requires C = 69·4; H = 10·2; N = 9·5 per cent.

Malonylbenzidine,



$$CH_2\!<\!\begin{matrix}CO\cdot NH\cdot C_6H_4\\ \vert\\ CO\cdot NH\cdot C_6H_4\end{matrix}.$$

Equimolecular quantities of ethyl malonate and finely powdered benzidine were heated together, in a flask provided with an air condenser, in a metal-bath at 210—220°. As soon as the ethyl malonate began to boil, alcohol could be detected escaping from the condenser. In a short time a solid commenced to separate in the flask, and soon the whole contents of the flask became solid. The condensation product proved to be practically insoluble in all the usual organic solvents and water. Any unchanged substance was removed by repeated extractions with boiling alcohol and acetone, and the bluish-grey residual powder finally heated at 100° to remove all traces of solvent:

0·1740 gave 0·4530 CO_2 and 0·0922 H_2O. C = 71·0; H = 5·9.
$C_{15}H_{12}O_2N_2$ requires C = 71·4; H = 4·76 per cent.

Di-α-carbethoxybutyrylbenzidine,

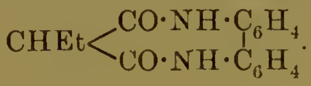
$CO_2Et\cdot CHEt\cdot CO\cdot NH\cdot C_{12}H_8\cdot NH\cdot CO\cdot CHEt\cdot CO_2Et$.

Ethyl ethylmalonate (1½ mols.) and benzidine (1 mol.) were heated together, as above, at 220—230°. In the course of about half an hour, the whole solution became a solid mass; this was crushed in a mortar, boiled with alcohol, and the whole filtered. The residue, when dry, did not melt at 300°. From the alcoholic filtrate, on cooling, three crops of a bluish-grey, flocculent solid were obtained. These were dissolved together in alcohol, filtered from some insoluble matter, and on slowly evaporating the filtrate, small, colourless, needle-shaped crystals were obtained, which melt at 189°, and are insoluble in dilute hydrochloric acid:

0·1280 gave 0·3146 CO_2 and 0·0796 H_2O. C = 67·0; H = 6·9.

$C_{26}H_{32}O_6N_2$ requires C = 66·6; H = 6·8 per cent.

Ethylmalonylbenzidine,



$CHEt<\begin{matrix}CO\cdot NH\cdot C_6H_4\\ CO\cdot NH\cdot C_6H_4\end{matrix}$.

The insoluble substance mentioned in the preparation of the last compound, which does not melt at 300°, was extracted several times with boiling acetone, and the residue dried at 100°:

0·1382 gave 0·3682 CO_2 and 0·0732 H_2O. C = 72·7; H = 5·9.

0·1236 „ 10 c.c. N_2 at 22° and 777 mm. N = 9·65.

$C_{17}H_{16}O_2N_2$ requires C = 72·9; H = 5·7; N = 10·0 per cent.

Diethylmalonylbenzidine.

Prepared from equimolecular quantities of ethyl diethylmalonate and benzidine. The alcoholic extract of the resulting condensation product deposited a bluish-grey, amorphous substance, which was again dissolved in alcohol to effect purification. It melted sharply at 224°:

0·1149 gave 0·3122 CO_2 and 0·0645 H_2O. C = 74·1; H = 6·3.

$C_{19}H_{20}O_2N_2$ requires C = 74·0; H = 6·5 per cent.

Propylmalonylbenzidine.

This is a grey, amorphous substance, practically insoluble in boiling alcohol and other organic solvents. It decomposes at 298°:

0·1277 gave 0·3335 CO_2 and 0·0737 H_2O. C = 71·2; H = 6·3.

$C_{18}H_{18}O_2N_2$ requires C = 73·5; H = 6·1 per cent.

Dipropylmalonylbenzidine.

This is a bluish-grey, amorphous substance, which melts at 264°.

Ethyl Decane-δδηη-tetracarboxylate,
$C_3H_7\cdot C(CO_2Et)_2\cdot CH_2\cdot CH_2\cdot C(CO_2Et)_2\cdot C_3H_7$.

This was prepared according to the method given by Lean (Trans., 1894, **65**, 1007) for the preparation of ethyl octane-γγζζ-tetracarboxylate ("ethyl diethylbutanetetracarboxylate"), the quantities used being 50 grams of ethyl butanetetracarboxylate (Perkin, Trans., 1894, **65**, 578), 6·6 grams of sodium in 80 grams of absolute alcohol, and 50 grams of propyl iodide. The ethereal extract left a clear brown oil, equal in weight to that of the ester taken, which crystallised on keeping. It was washed with light petroleum to remove any oil, and a pure substance was obtained without further crystallisation. On recrystallisation from dilute acetic acid, large, colourless, four-sided plates were obtained, which melted at 102—103°:

0·1286 gave 0·2892 CO_2 and 0·1032 H_2O. C = 61·3; H = 8·98.

$C_{22}H_{38}O_8$ requires C = 61·4; H = 8·8 per cent.

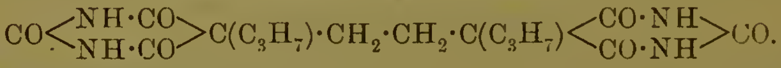
Decane-δδηη-tetracarboxylic Acid.

This crystallises from acetic acid in fine, colourless needles, which melt and decompose at 228°:

0·1477 gave 0·2843 CO_2 and 0·0900 H_2O. C = 52·5; H = 6·82.

$C_{14}H_{22}O_8$ requires C = 52·84; H = 6·9 per cent.

Ethylenebis-5-propylbarbituric Acid,



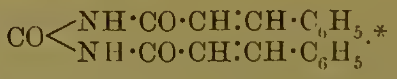
$$CO<\begin{matrix}NH\cdot CO\\ NH\cdot CO\end{matrix}>C(C_3H_7)\cdot CH_2\cdot CH_2\cdot C(C_3H_7)<\begin{matrix}CO\cdot NH\\ CO\cdot NH\end{matrix}>CO.$$

Ethyl decane-δδηη-tetracarboxylate (1 mol.), carbamide (3 mols.), and sodium (6 atoms) were condensed and worked up in the same manner as the malonamide condensations. The colourless solid obtained was crystallised from alcohol, and gave needle-shaped crystals, which did not melt at 300°:

0·1234 gave 0·2394 CO_2 and 0·0734 H_2O. C = 52·9; H = 6·6.
0·1824 „ 23·4 c.c. N_2 at 22° and 767 mm. N = 15·1.

$C_{16}H_{22}O_6N_4$ requires C = 52·5; H = 6·2; N = 15·3 per cent.

Dicinnamoylcarbamide,



$$CO<\begin{matrix}NH\cdot CO\cdot CH:CH\cdot C_6H_5\\ NH\cdot CO\cdot CH:CH\cdot C_6H_5\end{matrix}.^*$$

A mixture of cinnamoyl chloride (2 mols.) and carbamide (1 mol.) was gently heated in an oil-bath. When the temperature in the flask reached 100°, a vigorous reaction commenced, and hydrogen chloride was evolved. The reaction was soon over, and a solid mass remained, to which dry xylene was added, the mixture being heated to boiling for two hours. The hot xylene was then decanted, and the residue repeatedly extracted with boiling alcohol. A colourless powder was left, which was practically insoluble in all the usual organic solvents except acetic acid, from which it crystallised in clusters of small, colourless needles, which melted and decomposed at 246°:

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* During the course of this work some cinnamamide was required, and as no mention could be found in the literature of its formation having been attempted by means of the action of aqueous ammonia on the ester, some experiments were carried out in this direction. Five grams of ethyl cinnamate and 30 c.c. of

0·1147 gave 0·3020 CO_2 and 0·0514 H_2O. $C = 71·8$; $H = 5·0$.
$C_{19}H_{14}O_3N_2$ requires $C = 71·6$; $H = 5·0$ per cent.

Ethyl Cinnamoylcarbamate, $C_6H_5\cdot CH{:}CH\cdot CO\cdot NH\cdot CO_2Et$.

This substance has already been described by Diels and Heintzel (*Ber.*, 1905, **38**, 302), who prepared it by the action of ethyl cinnamate on ethyl sodiocarbamate. Whereas, however, the above authors obtained only 5 grams of crude product from 50 grams of ester, the method described here gives a yield of 48 per cent. of the cinnamoyl chloride used.

Cinnamoyl chloride (1 mol.) and urethane (2 mols.) were covered with dry benzene, which was heated to boiling for two hours. The benzene was then removed as far as possible by evaporation under diminished pressure, and the residue allowed to crystallise. Any unchanged urethane was extracted by vigorously stirring the dry, well-powdered product with water, and cinnamic acid was similarly removed by means of sodium carbonate solution. The residue was collected, washed well with water, and crystallised from dilute acetic acid. It formed colourless needles, melting at 108—109°. (Found, $N = 6·5$. Calc., $N = 6·4$ per cent.)

iso*Butyl Allophanate*, $NH_2\cdot CO\cdot NH\cdot CO_2\cdot CH_2\cdot CHMe_2$.

Cyanic acid, obtained by heating cyanuric acid, was bubbled through *iso*butyl alcohol kept cool by a freezing mixture. After passing gas for some time, the alcohol became cloudy, it was then filtered, and the filtrate allowed to evaporate spontaneously in the air. Crystals soon formed, and completely filled the liquid. They

concentrated ammonia (D 0·880) were shaken from time to time in a closed bottle. For nearly three weeks no apparent change took place, and then crystals began slowly to form in the ethyl cinnamate layer. After two months it was found that 1·89 grams of pure cinnamamide had been formed, which is equal to a 45 per cent. yield. In three months the yield had risen to 60 per cent., and in four months to 70 per cent. A pure specimen was obtained in large, hexagonal plates, which melted at 148—148·5° (corr.), the melting point given by Autenrieth (*Ber.*, 1901, **34**, 186) being 147°.

were collected and recrystallised from hot water, from which *isobutyl allophanate* separated in very fine, colourless needles, melting at 178—179°:

0·1708 gave 25·4 c.c. N_2 at 17° and 769 mm. N = 17·8.
$C_6H_{12}O_3N_2$ requires N = 17·5 per cent.

tert.-*Amyl Allophanate*, $NH_2\cdot CO\cdot NH\cdot CO_2\cdot CMe_2Et$.

Since preparing this compound, a description of its properties has appeared (D.R.-P. 226228). The melting point, however, is there given as 2° lower than that found by the author, namely, 151—152° (corr.), the substance decomposing a few degrees higher. The method of preparation was similar to that used in the case of *iso*butyl allophanate, except that the alcohol was not cooled, and the temperature allowed to rise to 70°.

Cinnamoyl-p-*aminoacetophenone*,
$C_6H_5\cdot CH{:}CH\cdot CO\cdot NH\cdot C_6H_4\cdot CO\cdot CH_3$.

Equimolecular quantities of cinnamoyl chloride, *p*-aminoacetophenone, and dry powdered potassium carbonate were mixed in a flask provided with a reflux condenser, covered with dry xylene, and heated to boiling for three hours in an oil-bath. The xylene, when cold, was decanted, and the residue washed, first with cold alcohol, and then warm water. The crude *cinnamoyl*-p-*aminoacetophenone*, which was left undissolved, was crystallised from acetic acid, and obtained in small, colourless needles, melting at 204—205°:

0·1309 gave 0·3654 CO_2 and 0·0662 H_2O. C = 76·2; H = 5·66.
$C_{17}H_{15}O_2N$ requires C = 76·6; H = 5·6 per cent.

α-*Bromo*iso*valeryl*-p-*aminoacetophenone*,
$CHMe_2\cdot CHBr\cdot CO\cdot NH\cdot C_6H_4\cdot CO\cdot CH_3$.

Equimolecular quantities of α-bromo*iso*valeryl chloride, *p*-aminoacetophenone, and dry powdered potassium carbonate were covered with dry benzene in a flask, and heated on the water-bath for an hour. After being kept at the ordinary temperature for twelve hours, the solution was filtered from inorganic matter, and evaporated to a small volume on the water-bath. On cooling, a mass of crystals separated, which, when collected and recrystallised from dilute acetic acid, formed colourless needles, melting at 113—114°:

0·1170 gave 0·2144 CO_2 and 0·0565 H_2O. C = 50·0; H = 5·4.
0·1614 „ 0·1037 AgBr. Br = 27·3.
$C_{13}H_{16}O_2NBr$ requires C = 52·35; H = 5·36; Br = 26·85 per cent.

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